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Docket No.: 3033.1003-001

U.S. Serial No. 09/909,348
Interview: February 17, 2004 at the USPTO
Steven Davis/Darrell Carney/ Examiner Hope Robinson

Claims

What is claimed is:

Claim 1 A method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor.

Claim 2 The method of Claim 1 wherein the site is an arthritic joint.

Claim 3 The method of Claim 1 wherein the site is being treated for cartilage damage or loss.

Claim 4 The method of Claim 1 wherein the site is being treated for cartilage damage or loss due to traumatic injury.

Claim 5 amended): The method of Claim 1 wherein the agonist is a peptide represented by the following structural formula:

Asp-Ala-R;

wherein R is a serine esterase conserved sequence.

Claim 6 The method of Claim 5 wherein the agonist is a peptide of between 12 and 23 amino acids.

Claim 7. The method of Claim 6 wherein the peptide comprises a *C*-terminal amide.

Claim 8 The method of Claim 7 wherein the serine esterase conserved sequence comprises of the amino acid sequence of SEQ ID NO.:1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof comprising at least six amino acids, provided that zero, one, two or three amino acids in the serine esterase conserved sequence differ from the corresponding position of SEQ ID NO.:1.

Claim 9 The method of Claim 7 wherein the serine esterase conserved sequence comprising the amino acid sequence of SEQ ID NO.:1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof consisting of at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved region are conservative substitutions of the corresponding amino acid in SEQ ID NO.:1.

Claim 10 The method of Claim 7 wherein the serine esterase conserved sequence comprising the amino acid sequence of SEQ ID NO.:2 (Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val, wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val), or a *C*-terminus truncated fragment of SEQ ID NO.:2, said fragment consisting of at least six amino acids.

Claim 11 The method of Claim 10 wherein the peptide comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO.:3).

Claim 12 The method of Claim 11 wherein the peptide comprises the amino acid sequence Arg-Gly-Asp-Ala-Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val (SEQ ID NO.:4), wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val.

Claim 13 The method of Claim 12 wherein the peptide comprises the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO.:5), or is an *N*-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the peptide differ from the amino acid at the corresponding position of SEQ ID NO.:5.

Claim 14 The method of Claim 12 wherein the peptide comprises the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5), or is an *N*-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the agoinst are conservative substitutions of the amino acid at the corresponding position of SEQ ID NO.:5.

Claim 15 The method of Claim 13 wherein the peptide is administered in a pharmaceutical composition additionally comprising an implantable, biocompatible carrier.

Claim 16 The method of Claim 15 wherein the carrier comprises a polylactic acid homopolymer, polyglycolic homopolymer or copolymer .

Claim 17 The method of Claim 12 wherein the peptide comprises the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5), or is an *N*-terminal truncated fragment thereof

Claim 18 A method of stimulating cartilage growth or repair at a site in a subject in need of such growth or repair, said method comprising the step of administering to the site a therapeutically effective amount of a *C*-amidet

23 amino acid peptide comprising the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5).

Claim 19 A method of stimulating cartilage growth at an arthritic joint in a subject, said method comprising the step of administering to the site a therapeutically effective amount of a *C*-terminal amidated 23 amino acid peptide comprising the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5).

Claim 20 A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss, said method comprising the step of administering to the site a therapeutically effective amount of a *C*-terminal amidated 23 amino acid peptide comprising the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5).

Claim 21 A method of stimulating cartilage growth in a subject at a site being treated for cartilage loss due to traumatic injury, said method comprising the step of administering to the site a therapeutically effective amount of a *C*-terminal amidated 23 amino acid peptide comprising the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val (SEQ ID NO.:5).

Claim 22 A method for culturing chondrocytes *in vitro*, the improvement comprising culturing the chondrocytes in the presence of a stimulating amount of an NPAR agonist.

Claim 23 The method of Claim 22, further comprising the step of administering a therapeutically effective amount of the cultured chondrocytes to a site in a subject in need of cartilage repair or growth.

Claim 24 The method of Claim 6, wherein the peptide is unsubstituted at the C-terminus.